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Antimicrobial treatment of invasive non-perinatal human listeriosis and the impact of the underlying disease on prognosis

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Abstract

Listeriosis is a resurgent foodborne disease in European countries. Benefits of combined β-lactam-aminoglycoside treatment remain controversial and the impact of the underlying disease on prognosis has not been fully assessed. We conducted a retrospective review of cases of sporadic listeriosis in adults from 1995 to 2008 at two university-affiliated hospitals serving a population of 600 000 people in Madrid, Spain. The primary end-point was the associated in-hospital mortality. Sixty-four patients were studied. Estimated incidence of listeriosis was 0.76/100.000 persons/year. Seventy-four per cent had chronic underlying diseases; cirrhosis of the liver and haematological and solid neoplasias were the most common comorbidities. Primary bacteraemia (58%) and meningitis (42%) were the most frequent manifestations. Focal infections were seen in ten cases. In-hospital mortality was 31%. Patients treated with ampicillin or with an ampicillin-gentamicin combination did not differ in age, severity of underlying disease or type of presentation. Differences in mortality were not seen between patients treated with monotherapy and those given combined treatment (28% vs 35%; p 0.634). Ten patients were treated with trimethoprim-sulfamethozaxole alone and only one died. All patients without comorbidities survived infection but mortality of patients with cirrhosis of the liver was 21% and that of patients with haematological or solid neoplasias was 66%. Only haematological neoplasia (OR 6.67; 95% CI 1.71–26.04; p 0.006) was significantly associated with an increased risk of mortality ($R^2_{\text{Cox–Snell}}$ = 0.262). Mortality of listeriosis mainly depended on the severity of the underlying disease. Combined ampicillin-gentamicin therapy did not improved survival. Trimethoprim-sulfamethozaxole may be an effective alternative therapy for listerial infections.

Keywords: Bacteraemia, *Listeria monocytogenes*, listeriosis, meningitis, septicaemia
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Introduction

Listeriosis is a resurgent foodborne disease caused by the bacterium *Listeria monocytogenes*. It has been estimated that 1850 cases occur annually in the USA [1]. In Western Europe the incidence of listeriosis has ranged from 0.3 to 0.8/100 000 persons/year in France and Italy respectively, although it seems to be increasing in the UK and other countries [2–5].

Listeria monocytogenes is found in soil, silage, water and a variety of raw foods such as meats or vegetables, and in processed foods such as soft cheeses and cold cuts [1,4]. It produces a severe disease characterized by septicaemia and meningitis with mortality rates from 20 to 50% [6]. Pregnant women can transmit the infection to the fetus, for whom the result can be fatal.

Several high-risk conditions for listeriosis have been identified. Malignancies, kidney disease and renal transplant, diabetes, alcoholism, increased age, liver disease and connective tissue disorders are the main predisposing factors [1,5]. In addition, patients with AIDS and those on treatment with tumour necrosis factor-α inhibitors also have an increased

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risk of listeriosis [7,8]. The susceptibility of healthy persons is substantially less than that of persons with underlying conditions. This predisposition is a consequence of suppressed T-cell-mediated immunity caused by the condition or its treatment [1].

Recommendations regarding therapy are based on data from *in vitro* tests, animal models and clinical experience. Penicillin and ampicillin are the preferred agents but because of delayed bactericidal activity against *Listeria*, most experts suggest adding gentamicin to ampicillin for the treatment of listeriosis [1,9]. Nonetheless, the benefits of combined treatment remain controversial and the effect of the underlying disease on prognosis may be of paramount importance.

The objectives of this investigation were to determine the incidence of listeriosis in adults in a metropolitan area of Madrid, and to assess the effect on mortality of adding gentamicin to β-lactam therapy. Because the severity of the underlying disease may be of even greater prognostic importance, an analysis of risk factors of mortality was also performed.

Patients and Methods

We conducted a retrospective review of a cohort of consecutive cases of sporadic listeriosis in adult patients from 1995 to 2008 at two university-affiliated hospitals serving a population of 600 000 people in Madrid.

Diagnosis was based on the isolation of *L. monocytogenes* from blood or cerebrospinal fluid. Bacterial identification was done following conventional methods [10]. Gram-positive, non-spore-forming rod, facultative anaerobes, that produced catalase and a narrow haemolysis and tumbling at 20–25°C were presumptively identified as *Listeria.* Further identification was by means of biochemical tests using API-Coryne; (BioMerieux, Marcy l'Etoile France). Susceptibility tests were performed following the CLSI recommendations [11].

Diagnosis of central nervous system infection was established on clinical grounds, cerebrospinal fluid analysis and when indicated by neuroimaging.

Listeriosis was considered hospital-acquired when signs of infection and isolation of *Listeria* occurred ≥72 h after admission.

Full daily doses of ampicillin (12 g) for adult patients with normal renal function were used. Gentamicin was used at doses of 1.5 mg/kg/8 h. For both antibiotics, dosage adjustments were made in patients with renal dysfunction.

The main measurement was the associated in-hospital mortality defined as death occurring before day 21 of hospitalization in association with listeriosis (septic shock, persisting sepsis, multi-organ dysfunction, brain damage). Deaths related to the underlying condition (e.g. progression of haematological neoplasia, gastrointestinal bleeding or hepatic encephalopathy) were not considered associated with listeriosis and were not entered in the final analysis. Age over 65 years, gender, chronic debilitating disease, cirrhosis of the liver, haematological neoplasia, solid neoplasia, immunosuppressive disease, bacteraemia, meningitis, ampicillin monotherapy and combined ampicillin-gentamicin were the variables considered in the analysis of risk factors of mortality.

Statistics

SPSS 16.0 was used for the statistical analysis of the data. Continuous variables were expressed as mean ± standard difference. Discrete variables were expressed as percentages. Association between qualitative variables was tested using chi-squared tests or Fisher exact test when sample size was small. Strength of association was measured by odds ratio (OR) or Haldane's estimator for small sample 2×2 tables and their 95% CI. Differences between groups were considered significant at $p < 0.05$.

Multivariate analysis was performed using a logistic regression model. The selection of variables for this multivariate analysis was performed by a forward-conditional method, with significance levels of ≤0.05 for inclusion and ≥0.1 for exclusion. Cox–Snell R^2 was used to assess the overall model fit.

Results

Sixty-four patients with sporadic invasive listeriosis were assessed. The estimated incidence was 0.76/100.000 persons/year. Patients had a mean age of 58.8 years, ranging from 19 to 86 years. Sixty-seven per cent were men.

Forty-seven (74%) had a chronic underlying disease. Cirrhosis of the liver (14 patients; 30%), other chronic disease such a diabetes, alcoholism or chronic renal failure (ten patients; 21%), haematological neoplasia (12 patients; 25%), solid neoplasia (six patients; 13%), and a miscellaneous group of immunocompromised hosts on high-dose corticosteroid therapy (five patients; 11%) were the most common comorbidities. Seventeen patients (26%) were adults without predisposing factors.

Listeriosis was acquired in the community in 47 instances (73%) and was hospital-acquired in 17 (27%). Hospital outbreaks were not observed and in cases in which listeriosis developed during hospitalization we did not identify a foodborne or other source of infection.

Primary bacteraemia (37 patients; 58%) and meningitis (27 patients; 42%) were the most common manifestations. Signs of meningoencephalitis or rhombencephalitis were observed

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in seven (26%) patients with central nervous system listeriosis. Focal, extraneural infections were seen in ten cases (16%): bacterial peritonitis in four, endocarditis in three and brain abscess in another three. Table 1 shows some clinical findings and outcome for these patients.

Table 2 lists the results of susceptibility tests of 46 isolates of *L. monocytogenes* to 13 antimicrobials.

Twenty patients died as consequence of listeriosis (31%). Most patients died in the first week of hospitalization from septic shock and multiorgan dysfunction or brain damage in association with listeriosis. Three of these patients who were empirically treated with inappropriate third-generation cephalosporins died during the first 48 h of admission in septic shock. These patients were excluded from the analysis of risk factors for mortality.

Patients were treated with ampicillin alone or in combination with gentamicin, or with trimethoprim-sulfamethoxazole. Generally, ampicillin or ampicillin plus clavulanate were started in combination with other antibiotics as part of an empiric regimen for sepsis and meningitis. Antimicrobial therapy was changed and other antimicrobials were stopped when isolation of *Listeria* was reported. Trimethoprim-sulfamethoxazole was initial therapy in some patients with meningitis in whom Gram stain of the cerebrospinal fluid showed Gram-positive bacilli or was given within the first 24 h after isolation of Gram-positive bacilli in blood cultures or cerebrospinal fluid.

Table 3 shows the results of treatment of listeriosis in adults. Patients treated with ampicillin alone or with ampicillin plus gentamicin did not differ in age (36% and 43% above 65 years, respectively), gender, severity of underlying disease or type of presentation. The number of patients without comorbidities (25% vs 39%), haematological or solid-organ cancer (25% vs 26%) and other chronic debilitating diseases (46% vs 26%) were not significantly different between the groups of patients. Differences in mortality were not seen (28% vs 35%, respectively; p 0.634).

Ten patients were treated with only trimethoprim-sulfamethoxazole. Table 4 shows the most relevant clinical findings observed in these individuals. Significant differences in mortality were not recorded among patients treated with ampicillin and trimethoprim-sulfamethoxazole (28% vs 10%, respectively; p 0.396).

Mortality varied according to the underlying condition. Whereas all patients without comorbidities survived infection, mortality of patients with haematological and solid neoplasias was 66% (eight out of 12 and four out of six, respectively). Mortality in patients with cirrhosis and other chronic debilitating diseases was 21.4% and 20%, respectively. Haematological neoplasia (OR 14.4; p 0.001), solid neoplasia (OR 14.4; p 0.007) and immunosuppressive disease (OR 10.8; p 0.021) were associated with mortality.

TABLE 2. Susceptibility of *Listeria monocytogenes* to various antimicrobials

Agent	Minimal inhibitory concentration mg/L		
	Range	MIC_{50}	MIC_{90}
Benzylpenicillin	0.06–0.5	0.25	0.5
Erythromycin	0.12–0.25	0.12	0.25
Clarithromycin	0.12	0.12	0.12
Azithromycin	0.25–1	0.5	1
Doxycycline	0.06–0.25	0.12	0.25
Josamycin	1–4	2	2
Lincomycin	2–128	8	16
Vancomycin	0.25–1	1	1
Teicoplanin	0.2 5–0.5	0.25	0.5
Rifapentine	0.03–64	0.06	0.12
Quinupristin-dalfopristin	2–16	4	4
Levofloxacin	0.25–2	0.5	1
TMP-SMZ	0.06–0.5	0.5	0.5

46 strains tested.

TABLE 3. Results of the treatment of listeriosis with different antimicrobials and combinations

Antimicrobials	Treated, *n*	Died, *n* /(%)	Survived, *n* /(%)
Ampicillin alone	28	8 (28)	20 (72)
Ampicillin plus gentamicin	23	8 (35)	15 (65)
Trimethoprim-sulfamethoxazol	10	1 (10)	9 (90)
Other regimens[a]	3	3 (100)	

No differences for comparisons of ampicillin alone vs ampicillin plus gentamicin (p 0.634) or ampicillin vs TMP-SMZ (p 0.396).
[a]Third-generation cephalosporins.

TABLE 1. Clinical findings and outcome of patients with focal, extra-meningeal infections caused by *Listeria monocytogenes*

Patient	Age/sex	Underlying condition/focal infection	Manifestations	Treatment	Outcome
1	75/M	Liver cirrhosis/primary bacterial peritonitis	Fever, abdominal pain, diarrhoea	A + G	Cured
2	69/M	Liver cirrhosis/primary bacterial peritonitis	Fever, abdominal pain, hepatic encephalopathy	A + G	Cured
3	59/M	Liver cirrhosis/primary bacterial peritonitis	Fever, abdominal pain, hepato-renal syndrome	A	Died
4	62/M	Liver cirrhosis/primary bacterial peritonitis	Fever, abdominal pain, hepatic encephalopathy	A	Cured
5	60/M	Liver cirrhosis/brain abscess.	Fever, headache, hemiparesis	TMP-SMZ	Cured
6	36/M	Non-Hodgkin's lymphoma/brain abscess	Fever, seizures, septic shock	A	Died
7	71/M	Wegener granulomatosis/brain abscess	Fever, seizures, confusion	A + TMP-SMZ	Cured
8	74/M	Aortic prosthesis/PVE	Fever, peripheral emboli	A + G	Cured
9	77/M	Aortic prosthesis/PVE	Fever, heart failure	A + G + VR	Cured
10	68/M	Mitral prosthesis/PVE	Fever, heart failure	A + G + VR	Cured

M, male; F, female; A, ampicillin; G, gentamicin; TMP-SMZ, trimethoprim-sulfamethoxazole; PVE, prosthetic valve endocarditis; VR, valve replacement.

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TABLE 4. Summary of clinical findings and outcome of patients with invasive listeriosis treated with trimethoprim-sulfamethoxazole

Patient	Age/sex	Underlying disease	Manifestation	Outcome
1	31/M	Non-Hodgkin lymphoma	Bacteraemia	Lived
2	29/F	Acute leukaemia	Bacteraemia	Lived
3	70/M	None	Meningitis	Lived
4	81/M	Cirrhosis of the liver	Bacteraemia	Lived
5	60/M	Cirrhosis of the liver	Brain abscess	Lived
6	68/M	Diabetes mellitus, CRF	Meningitis	Lived
7	69/M	Alcoholism, diabetes	Bacteraemia	Lived
8	68/F	SLE, C&E treatment	Bacteraemia	Lived
9	50/F	Cirrhosis of the liver	Meningitis	Lived
10	70/F	Myelocytic leukaemia	Meningitis	Died

CRF, chronic renal failure; SLE, systemic lupus erythematosus; C&E, corticosteroid therapy.

In the multivariate analysis, only haematological neoplasia (OR 6.67; 95% CI: 1.71–26.04; p 0.006) was significantly associated with an increased risk of mortality ($R^2_{Cox–Snell}$ = 0.262). Age over 65 years (p 0.084), sex (p 0.802), chronic debilitating disease (p 0.164), cirrhosis (p 0.519), haematological neoplasia (p 0.006), solid neoplasia (p 0.071), immunosuppressive disease (p 0.171), bacteraemia and meningitis (p 0.394), ampicillin monotherapy (p 0.967) and combined ampicillin-gentamicin (p 0.781) were not independent factors for mortality.

Discussion

In recent years an increasing rate of listeriosis has been reported in some European countries [3,5]. These increases primarily reflect a higher rate of bacteraemic listeriosis in the elderly, and are not otherwise correlated with geography, socioeconomic status or serotypes [3]. However, in the USA, non-perinatal listeriosis-associated deaths have decreased, paralleling a decreasing trend in incidence [12]. From our investigation it seems clear that the incidence of invasive listeriosis in Madrid was equivalent to that observed in other European countries and parts of Spain [2,13].

There is compelling evidence that invasive listeriosis is mainly a disease of people with a variety of chronic conditions including severe immunosuppressive disorders [5,14]. Cirrhosis of the liver, diabetes mellitus, chronic renal failure, haematological and solid-organ neoplasia, and treatment with corticosteroids were the most common factors predisposing for listeriosis. The absence of AIDS as a high-risk condition in our study might reflect the generalized use of trimethoprim-sulfamethoxazole in patients with severe $CD4^+$ lymphocyte depletion [7]. By the same token, trimethoprim-sulfamethoxazole given for prophylaxis of *Pneumocystis jirovecii* infection, has been reported to be an effective preventive therapy for listeriosis in solid-organ transplant recipients [15].

Primary bacteraemia and meningoencephalitis were the predominant manifestations of listeriosis [1,14,16]. Of interest was the occurrence of focal, extracranial involvement by *Listeria* in 16% of our cases, a percentage equivalent to that observed by others [16]. Bacterial peritonitis in patients with cirrhosis, and brain abscess and endocarditis in patients with prosthetic valves were the most common infections observed in this and other series [7,16].

Currently, listeriosis is frequently a nosocomial infection and from 16% to 30% of cases are hospital-acquired [16,17]. Twenty-seven per cent of patients in this series developed listeriosis during hospitalization for other diseases. Cases occurred sporadically without temporal aggregation and we did not find a hospital source of listeriosis in these patients. All cases occurred within the first 2 weeks of hospitalization, a short time that makes unlikely the nosocomial acquisition of listeria, which may have an incubation period up to 1 month [18]. Because faecal asymptomatic carriage is not uncommon [1,17], we suggest that colonization could have occurred before hospitalization and infection then developed after admission, favoured and triggered by increased immunosuppression, antibiotic therapy, alkalinization of the stomach by antiacids or some other circumstances.

Mortality from listeriosis remains high, ranging from 20% to 38% in most recent series [14–17,19,20]. Nevertheless, data on risk factors for mortality are limited. Guevara *et al.* [14] found that non-haematological malignancy, alcoholism, steroid medication, and kidney disease were risk factors for mortality. Patients admitted to the hospital with a diagnosis of sepsis alone had the highest mortality [14]. Others found renal failure, corticosteroid therapy and hospital-acquired infection associated with a poor prognosis [16]. Severe immunosuppression and infection caused by serotype 4b have also been implicated in fatal prognosis [21,22].

Age above 70 years has been considered an important risk factor for mortality [14]. However, Gerner-Smidt *et al.* [22] found that age was not a significant risk factor for mortality, but was an effect modifier of the risk associated with underlying illness. Among patients aged below 70 years, a condition known to predispose to listeriosis was an important risk factor for mortality but this was not the case for patients

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over 70 years, whose risk of mortality was independent of other conditions [22]. In our series, age was not an independent factor associated with mortality. Mortality from listeriosis seemed to depend most directly on the severity of the underlying disease and haematological neoplasia was significantly associated with an increased risk of death. As shown by others, patients with solid-organ neoplasia and those who were immunosuppressed as the result of corticosteroid therapy also exhibited high rates of mortality [14,15,22]. This is in sharp contrast with the favourable prognosis of listeriosis in adults without predisposing conditions.

The effect of the kind of treatment on prognosis of listeriosis remains controversial. Because *in vitro* and *in vivo* ampicillin monotherapy produces a suboptimal response, combination of ampicillin with gentamicin has been the preferred treatment in clinical practice [1,9,19]. However, renal failure is frequently found in patients with listeriosis and those with cirrhosis or diabetes are prone to develop renal failure during gentamicin therapy [16]. For these reasons, the role of aminoglycoside in the treatment of listeriosis must be re-evaluated.

Mitja *et al.* [16] found that among 102 patients with listeriosis, 32% were treated with ampicillin plus gentamicin and 68% received monotherapy with ampicillin. Both groups were equivalent in terms of age, underlying disease, type of presentation and other factors. Mortality was higher in patients treated with the combination of ampicillin and aminoglycosides than in those with ampicillin monotherapy, although the results did not reach significance. Hence, in this investigation gentamicin did not decrease early mortality but seemed to increase it [16]. Similarly in our study, we did not find differences in mortality among patients with listeriosis treated with ampicillin monotherapy and those given combined treatment.

Susceptibility of *L. monocytogenes* to penicillins and other antimicrobial agents has remained unchanged and most isolates are susceptible to a wide variety of antimicrobials [23,24]. The prevalence of resistant strains was estimated at 1.27% among clinical isolates [25].

Trimethoprim-sulfamethoxazole is bactericidal for *Listeria* [23]. However, only a few cases of listeriosis treated with trimethoprim-sulfamethoxazole have been reported so far [26]. In patients with meningitis who had a rapid clinical response to therapy, trimethoprim-sulfamethoxazole has been successfully used to extend antimicrobial therapy in the outpatient setting [27]. The combination of trimethoprim-sulfamethoxazole plus ampicillin was associated with a much lower failure rate and fewer neurological sequelae than ampicillin combined with gentamicin [28]. In our experience, trimethoprim-sulfamethoxazole was effectively used in patients with listeriosis and 90% of patients with bacteraemia and/or meningitis were cured. Two patients with brain abscess were treated with trimethoprim-sulfamethoxazole alone or combined with high-dose ampicillin and both had an uneventful recovery without neurological sequelae. We believe that trimethoprim-sulfamethoxazole is a safe and useful alternative therapy for patients with invasive listeriosis. Trimethoprim-sulfamethoxazole has bactericidal extracellular and intracellular activity against *Listeria* and excellent central nervous system penetration, and so may be effective for the treatment of refractory listeriosis.

Our study has some limitations. Basically, it is a retrospective study considering a relatively small number of cases seen over a period of 14 years and some uncontrolled factors could have confounded our results. The potential for differential care among these hospitalized patients is likely to be minimal because all patients were seen by a small number of healthcare providers with similar training and prescription habits and who use the same diagnostic and therapeutic tools. They can, therefore, be considered a homogeneous group in this respect.

Our findings suggest that underlying conditions themselves appear to be more important than the kind of treatment in determining prognosis. The findings of this study should highlight the importance of certain underlying conditions, particularly haematological neoplasia, and their association with high mortality rates. Because factors determining outcome seem unchangeable, prevention must be reinforced.

The number and diversity of conditions that appear to increase the risk and mortality of listeriosis imply that healthcare providers should consider listeriosis when treating patients with concurrent conditions and provide appropriate food safety advice [29].

Transparency Declaration

No conflicts of interest declared.

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